REMARKS

After entry of this Amendment, claims 113, 117-120, 123, 125, 129-135, 137-139, 141-144, 170-174, 180-182, 185, 187, 190-195, 197-204, 206-209, 235-239, 241-242, 251 and 254-273 will be pending in this application.

Applicants have amended claims 113, 117, 130, 143, 172, 182, 193, 199, 201, 208, 235 and 251 to improve their form. Applicants respectfully submit that these amendments do not add new matter to the specification.

Applicants have added claims 258-273. Applicants respectfully submit that claims 258-273 do not add new matter to the specification. Support for claims 258, 262, 266 and 270 can be found on page 41, line 5. Support for claims 259-261, 263-265, 267-269 and 271-273 can be found on page 13, lines 3-21, page 19, lines 5-6 and page 16, lines 1-3.

Rejection Under 35 U.S.C. §102

The Examiner has rejected claims 113, 117-120, 123, 131-135, 137-139, 141-144, 170-174, 180-182, 185, 187, 190, 193-195, 197-204, 206-209, 235-239, 241-242, and 251 under 35 U.S.C. §102(e) in view of U.S. Patent No. 5,532,159 to Webb et al. ("*Webb*"). The Examiner states that the rejection over *Webb* is maintained for the reasons of record. The Examiner further states that the "disclosed examples and preferred embodiments [in *Webb*] do not necessarily constitute a teaching away from a broader disclosure or non-preferred embodiments." The Examiner states that because the experiments disclosed in *Webb* were conducted in nude mice, "it would be difficult to observe the normal physiological and immunological effects that occur with the humoral and cell-mediated response." The Examiner concludes by stating that Applicants' arguments "are not entirely relevant because the prior art example does not adequately parallel the scope of the claims."

Applicants continue to traverse the Examiner's rejection over *Webb*. *Webb* provides a monoclonal antibody that specifically binds OFP, a cancer cell product, for the treatment of cancer. *Webb* indicates that an anti-tumor response is observed within ***one day*** after the administration of one dose of the anti-OFP antibody. *Webb* states: "It is believed that OFP is immunosuppressive and by sequestering or removing OFP via monoclonal antibody, the

patient's immune defense against tumors is released from impairment allowing a more efficient and natural rejection of cancer." (*See Webb*, col. 2, lines 56-60; *see also* col. 3, lines 62-65.)

The pending claims recite a method for inducing a therapeutic host immune response against a multi-epitopic *in vivo* antigen comprising administering a composition comprising a binding agent and allowing the binding agent to form a binding agent/antigen pair, "whereby an effective host T cell response is elicited against the antigen on the binding agent/antigen pair" (*see, e.g.*, claims 113 and 135), or "wherein the binding/antigen complex elicits an effective host humoral immune response against a second epitope of the [] antigen" (*see, e.g.*, claims 174 and 201). There is absolutely no evidence that the method disclosed in *Webb* induces a therapeutic host immune response resulting in an effective host T cell response against the antigen on the binding agent/antigen pair, or resulting in a host humoral immune response against a second epitope of the antigen. In fact, as discussed in further detail below, ***all*** of the evidence indicates that the antibody used in *Webb* does ***not*** elicit an effective host T cell or humoral immune response against the antigen. Accordingly, *Webb*, when considered as a whole, does not teach all of the limitations of the pending claims.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987), MPEP § 2131. In order to prove that an element is "inherent" in the prior art, "the evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference." *Id.* "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP § 2112 (emphasis in original). It has long been recognized that inherency cannot be established by probabilities or possibilities. When relying on a theory of inherency, "the examiner must provide evidence that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." *Id.* (emphasis in original).

Webb indicates that an anti-tumor response is observed within ***one day*** after the administration of one dose of the anti-OFP antibody. (*See* Figure 1 (showing that anti-OFP antibody is administered on day 7 of the protocol and tumor volume is decreased on day 8) and

column 11, lines 27-29.) As Applicants explained in their previously filed response, a host T cell response or a host humoral immune response takes ***more than one day*** to develop. (*See* Applicants' arguments in the Reply filed 5/19/04, including Exhibits A-C attached thereto.) Thus, the antibody disclosed in *Webb* cannot be causing an anti-tumor effect by enhancing a host T cell immune response or humoral immune response against the antigen. Further, the anti-OFP antibody used in *Webb* has an anti-tumor effect in nude mice, deficient in functional T cells that are unable to mount a functional T cell response. This includes a helper T cell response, which is required to elicit an effective humoral response.

Moreover, *Webb* discloses that treatment with a mixture of anti-OFP antibody and excess OFP antigen, which did not inhibit, and in fact appeared to accelerate, the growth of mammary tumors in Sprague Dawley rats. (*See Webb*, column 11, lines 53-59). If an immune response were elicited against the OFP antigen in the OFP/anti-OFP antibody binding pair, one would expect the administration of anti-OFP antibody and OFP antigen to elicit the same immune response and show an anti-tumor effect; this is clearly not the case. Accordingly, this data supports Applicants' position that the anti-OFP antibody causes an anti-tumor response by removing OFP from circulation and not by eliciting an immune response against the antigen. When the anti-OFP antibody is administered with excess OFP antigen, the anti-OFP is pre-bound to antigen and therefore unable to bind and remove the circulating OFP antigen.

Finally, *Webb* is completely silent about the use of disclosed monoclonal antibody to form a binding agent/antigen complex, which elicits an immune response against a ***second*** epitope of a multi-epitopic antigen (as required by claims 174 and 201, and the claims dependent thereon).

The Examiner appears to base his rejection on a theory of inherent anticipation. As discussed above, *Webb* indicates that OFP is immunosuppressive and that the observed anti-tumor effect of the anti-OFP antibody is believed to be caused by sequestering or removing OFP from the blood, thereby releasing the patient's immune defense against tumors from impairment and allowing a more efficient and natural rejection of cancer. (*See Webb*, col. 2, lines 56-60; *see also* col. 3, lines 62-65.) In a previous Office Action (dated March 15, 2004), the Examiner stated that the immune response is not predictable and discrete and that, therefore, the statements

made in *Webb* regarding the mechanism of action of the anti-OFP antibody do not remove the possibility that other mechanism are responsible for the observed anti-tumor effects. The Examiner states: "There are hundreds of possible biological processes, events, and mediators that ***may*** account for an observed humoral and or cell-mediated response. Thus, even if the anti-OFP-complex is removed, its removal does not eliminate the ***possibility*** that a different or second OFP epitope was exposed to the immune system, thus facilitating an anti-tumor response." (Office Action dated 3/15/04; page 4, emphasis added.) Applicants respectfully submit that the Examiner's arguments that the antibody disclosed in *Webb* ***may*** elicit the claimed therapeutic immune responses are insufficient, as a matter of law, to establish anticipation under a theory of inherency. As discussed above, inherency cannot be established by probabilities or possibilities. The MPEP states that "[w]hen relying on a theory of inherency, the examiner must provide evidence that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." MPEP §2112 (emphasis in original). The Examiner has not provided any evidence that the anti-OFP antibody disclosed in *Webb* necessarily elicits the claimed host T cell and humoral immune responses. Indeed, to the contrary, the evidence indicates that it does not. The absence of any teaching or evidence in *Webb* regarding the elicitation of a host T cell or humoral immune response, let alone a response to a second epitope, cannot be ignored.

The Examiner's statement that the "examples and preferred embodiments [in *Webb*] do not necessarily constitute a teaching away from a broader disclosure or nonpreferred embodiments" is inapplicable because *Webb* does not contain any broad disclosure of the use of anti-OFP antibodies to enhance the host T cell or humoral immune response against the antigen. Moreover, the fact that "the prior art example does not adequately parallel the scope of the claims" is very relevant since it is the differences between the cited art as a whole (including the examples) and the claims of the instant application that render the claimed invention novel.

Additionally, the Examiner points out that the data illustrated in Fig. 1 of *Webb* was obtained from nude mice and, therefore, "it would be difficult to observe the normal physiological and immunological effects that occur with the humoral and cell-mediated response." Applicants point out that ***in addition*** to the data presented in Fig. 1, *Webb* presented evidence that mammary tumors induced in female Sprague Dawley rats could be reduced within one day after the administration of the anti-OFP antibody. (*Webb* states (col. 11, lines 27-29):

"In essentially all cases, the tumor volume decreased within one day after injection of the MOFP-A [anti-OFP antibody], as shown in Table 1.") Accordingly, the Examiner cannot discount all the data presented in *Webb* as irrelevant.

Finally, *Webb* shows that the anti-tumor effect of the anti-OPF antibody is observed after the administration of a single dose of antibody (*see* col. 11, lines 24-25; col. 12, lines 5-6, 46-47 and 58-59); whereas Applicants teach multiple administrations of antibody (*see, e.g.*, claims 258, 262, 266 and 270).

Applicants submit that, when considered as a whole, *Webb* does not disclose each and every limitation of the pending claims either explicitly or inherently.

In view of all of the arguments of record, including the arguments presented herein, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection Under 35 U.S.C. §103

The Examiner has rejected claims 113, 117-120, 123, 125, 129-135, 137-139, 141-144, 170-174, 180-182, 185, 187, 190-195, 197-204, 206-209, 235-239, 241-242, 251 and 254-257 under 35 U.S.C. §103(a) as allegedly unpatentable over Baum et al. (Hybridoma 12(5):583-589 (1993)) ("*Baum*") or Madiyalakan et al. (Hybridoma 14(2): (1995)) ("*Madiyalakan*") in view of *Webb*.

Applicants respectfully traverse. First, there is no motivation to combine the teachings of *Webb*, *Baum* and *Madiyalakan*. Further, even if the references were combined (albeit improperly), the combination of references still does not disclose or suggest all of the limitations of the pending claims. The deficiencies of *Webb* have been discussed *supra,* and cannot be cured by *Baum* or *Madiyalakan*. Both *Baum* and *Madiyalakan* teach the use of radiolabeled antibodies or radiolabeled antibody fragments. Both of these references teach that the radionuclide is the toxic agent, and that the antibody or antibody fragment is merely a targeting mechanism -- not the basis for the therapeutic effect. Thus, none of the cited references teach the use of a binding agent specific for a multi-epitopic antigen to form an antigen/binding agent pair that is capable of enhancing the host T cell or humoral immune response against the antigen.

For the reasons discussed above, the cited references do not render obvious the pending claims, and Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection Under 35 U.S.C. 112, first paragraph

The Examiner has rejected claims 190 and 238 stating that the claim term "non-human" does not have support in the specification as originally filed, and fails to meet the written description requirement.

Applicants continue to traverse this rejection. MPEP § 2163.02 states: "The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirements." All that is required is that the specification allows a person of ordinary skill in the art to recognize that the inventor was in possession of the claimed invention at the time that the application was filed. The specification discloses the use of antibody B43.13, which is a murine (non-human) antibody, in the claimed methods. Accordingly, the specification as originally filed clearly provides for the use of "non-human" antibodies in the claimed invention and shows that Applicants were in possession of this invention at the time that the application was filed. Applicants respectfully request reconsideration and withdrawal of this rejection.

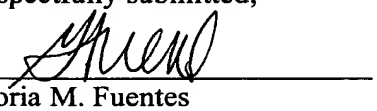
Concluding Remarks

In view of the amendments and arguments made herein, Applicants believe the pending application is in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner believes that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Applicants believe no fee, other than the fee for the Petition for a three-month extension of time, is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw, under Order No. AREX-P03-004.

Dated: May 16, 2005

Respectfully submitted,

By 

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